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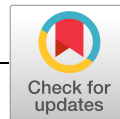
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REVIEW ARTICLE

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Small molecule inhibitors of epithelial-mesenchymal transition for the treatment of cancer and fibrosis

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Abstract

Tissue fibrosis and cancer both lead to high morbidity and mortality worldwide; thus, effective therapeutic strategies are urgently needed. Because drug resistance has been widely reported in fibrotic tissue and cancer, developing a strategy to discover novel targets for targeted drug intervention is necessary for the effective treatment of fibrosis and cancer. Although many factors lead to fibrosis and cancer, pathophysiological analysis has demonstrated that tissue fibrosis and cancer share a common process of epithelial-mesenchymal transition (EMT). EMT is associated with many mediators, including transcription factors (Snail, zinc-finger E-box-binding protein and signal transducer and activator of transcription 3), signaling pathways (transforming growth factor- β 1, RAC- α serine/threonine-protein kinase, Wnt, nuclear factor-kappa B, peroxisome proliferator-activated receptor, Notch, and RAS), RNA-binding proteins (ESRP1 and ESRP2) and microRNAs. Therefore, drugs targeting EMT may be a promising therapy against both fibrosis and tumors. A large number of compounds that are synthesized or derived from natural products and their derivatives suppress the EMT by targeting these mediators in fibrosis and cancer. By targeting EMT, these compounds exhibited anticancer effects in multiple cancer types, and some of them also showed antifibrotic effects. Therefore,

drugs targeting EMT not only have both antifibrotic and anticancer effects but also exert effective therapeutic effects on multiorgan fibrosis and cancer, which provides effective therapy against fibrosis and cancer. Taken together, the results highlighted in this review provide new concepts for discovering new antifibrotic and antitumor drugs.

KEYWORDS

cancer, epithelial-mesenchymal transition, fibrosis, natural product, small molecule, transcription factor, tumor

1 | INTRODUCTION

Tissue fibrosis and cancer are two major causes of high human morbidity and mortality worldwide. Although there are multiple therapies for cancer, including chemotherapy, oncologic surgery, and radiation therapy, an effective therapeutic strategy is needed.¹ Among these therapeutic strategies, chemotherapy is the main tool for curing various cancers. The therapeutic resistance of anticancer drugs, such as 5-fluorouracil, gemcitabine, gefitinib, and trastuzumab, has been widely observed in the clinic.² However, due to the lack of effective therapeutic drugs, tissue fibrosis still threatens human health. Although some drugs exhibit antifibrotic effects, including angiotensin-converting enzyme inhibitors, aldosterone inhibitors, statins, angiotensin II type 1 receptor blockers, endothelin receptors, β -blockers, acetylsalicylic acid, and matrix metalloproteinase (MMP) inhibitors, none of them are specifically designed to target fibrosis, and the related side effects limit their clinical use for treating fibrosis.^{3–6} Thus, antifibrotic and anticancer treatments are extremely urgent, and new therapeutic drugs should be designed based on specific targets that contribute to the progression of fibrosis and tumors.

Epithelial-mesenchymal transition (EMT) is a reversible terminal differentiation process in which epithelial cells shed their properties and acquire a more mesenchymal phenotype.⁷ EMT is a fundamental process widely involved in the development and the progression of various diseases, and there are mainly three types of EMT⁸ (Figure 1). Type I EMT is involved in embryonic development and organ formation. Type II EMT is critical for wound healing and fibrosis. Type III EMT contributes to the progression and metastasis of tumors.⁹ Extensive studies revealed that EMT profoundly contributed to the production of myofibroblasts, which are the major cells producing massive amounts of collagen that leads to the deposition of collagen in the development of fibrosis.¹⁰ In addition, EMT confers increased motility and invasiveness in epithelial-derived tumor cells and promotes tumor metastasis. Therefore, fibrosis and tumors share the common process of EMT, and drugs that specifically target EMT may exhibit both antifibrosis and antitumor effects, which will provide an effective strategy against fibrosis and tumors.

Small molecules have a long history of acting as drugs for the treatment of hypertension, infections, heart failure, diabetes, asthma, rhinitis, and tumors and comprise approximately 75% of the anticancer drugs approved by the FDA from 1981 to 2014.¹¹ Recently, many small molecules target EMT and exhibit good therapeutic effects on retarding progressive tissue fibrosis and cancer in experimental conditions.^{12–14} In addition, it is worth noting that many small molecules, such as tivantinib, trametinib, linsitinib, nintedanib, and binimetinib, are in ongoing clinical trials for the treatment of tumors.² These cases show promising prospects for treating fibrosis and cancer, which encourages researchers to find effective small molecule drugs for treating fibrosis and cancer.

In this review, we describe some important transcription factors, signaling pathways, RNA-binding proteins and microRNAs (miRNAs) and several novel regulators that contribute to EMT and further present some small

molecules that exhibit therapeutic effects against EMT. Targeting these mediators with these compounds may be a promising therapeutic strategy to treat fibrosis and cancer.

2 | SMALL MOLECULES AGAINST EMT

Several excellent reviews have discussed the mechanisms of EMT well.¹⁵ Briefly, histological and pathological analyses show that epithelial cells are present in single cell layers or multilayers and show apical-basal polarity. Epithelial cells not only interact with the basement membrane with integrins but also communicate with each other via specialized intercellular junctions, including desmosomes, subapical tight junctions, adherens junctions and scattered gap junctions. These interactions help maintain epithelium integrity and function. However, some stimuli drive EMT in pathological conditions. During the process of EMT, epithelial cell-cell junctions are dissolved, and the epithelial cells lose their apical-basal polarity and acquire front-rear polarity. In addition, the cytoskeletal architecture is reorganized, and E-cadherin expression is replaced by N-cadherin expression, which enhances cell motility and invasiveness. In fibrosis, mesenchymal-like cells transform into myofibroblasts, which can be activated to produce excessive collagen, and in tumors, these mesenchymal-like cells migrate along with the circulatory system to a secondary location where they form a secondary tumor via mesenchymal-epithelial transition (MET).¹⁶ It is worth noting that tissue fibrosis and tumors share the common process of EMT, which suggests that targeting EMT may be an effective strategy to treat both fibrosis and tumors (Figure 1). EMT is regulated by various mediators such as transcription factors, signaling pathways, RNA-binding proteins, and miRNAs. In addition, there are many small molecules that exhibit effective therapeutic effects on tissue fibrosis and tumors by suppressing EMT via targeting these mediators.

2.1 | Inhibition of transcription factors by small molecules

Transcription factors such as Snail, Twist, zinc-finger E-box-binding homeobox (ZEB) and signal transducer and activator of transcription 3 (STAT3) are activated early and play central roles in the EMT. They not only repress the epithelial phenotype but also activate the mesenchymal phenotype individually or by cooperating with other transcription factors. Thus, inhibiting the activation of transcription factors may be an effective way to block EMT to treat fibrosis and tumors. Indeed, many compounds significantly intervene in fibrosis and tumors by suppressing the activation of transcription factors.

2.1.1 | Snail transcription factors

Snail is a zinc-finger transcriptional repressor that consists of three isoforms, Snail1, Snail2, and Snail3. Among them, Snail1 and Snail2 are activated in the EMT during development, fibrosis, and cancer. The upregulation of Snail1 is found in many different types of cancer such as gastric, colorectal, and prostate cancer.¹⁷⁻¹⁹ In addition, the overexpression of Snail1 enhanced the motility and invasion of prostate cancer cells, and the silencing of Snail remarkably suppressed the adhesion, migration, and invasion of Hep-2 cells.¹⁹ Further study revealed that the knockdown of Snail blocked the EMT, which was accompanied by the downregulation of the expression of MMP-2, MMP-9, vimentin, N-cadherin, and fibronectin.¹⁹ Moreover, Snail expression was demonstrated at different stages of kidney fibrosis, and the reactivation of Snail-induced renal fibrosis²⁰ (Figure 2). Furthermore, hypoxia-inducible factor 1 α (HIF-1 α) mediated EMT by regulating Snail and the β -catenin signaling pathway in early pulmonary fibrosis induced by paraquat.²¹ Based on these findings, it was suggested that Snail played a key role in the EMT during fibrosis and cancer, and the targeted inhibition of Snail expression might be an effective therapy to treat fibrosis and tumors.

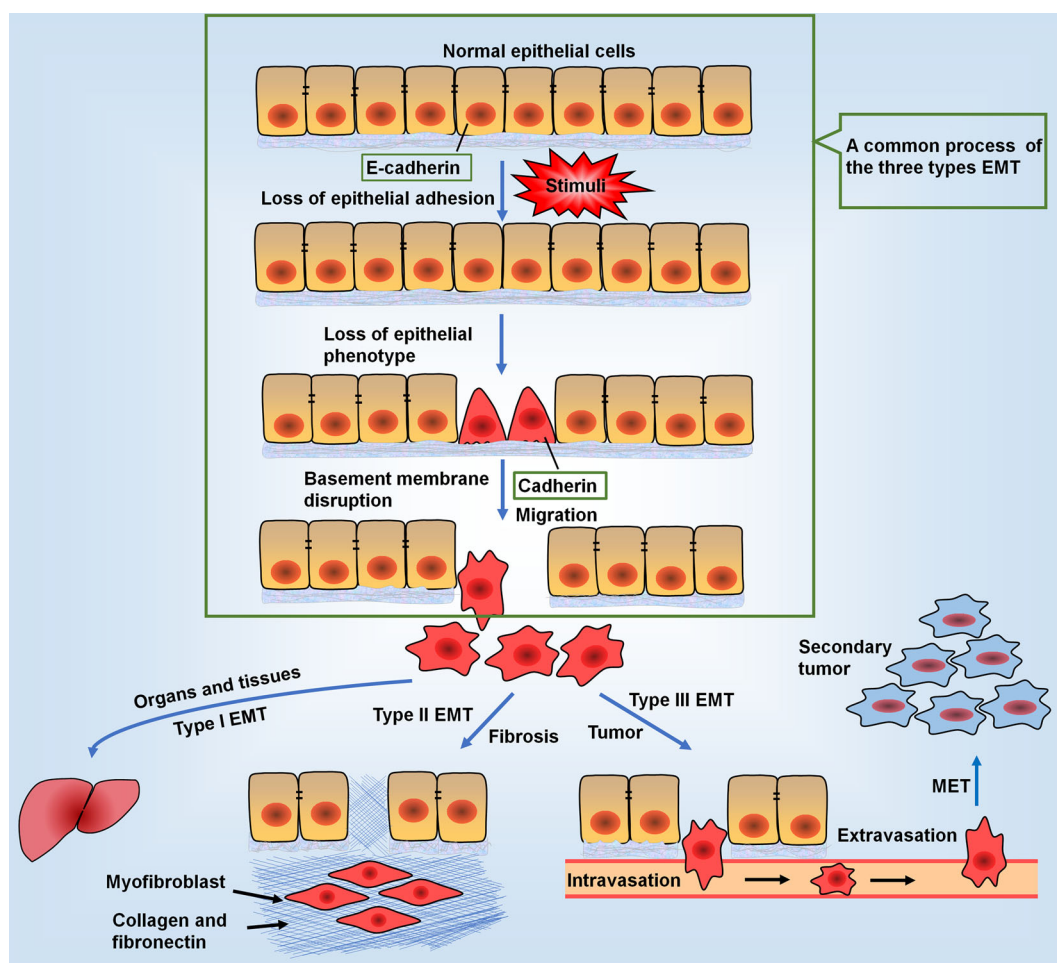


FIGURE 1 Cellular events during EMT. Under normal conditions, epithelial cells exist as single cell layers or multilayers and communicate with each other via specialized intercellular junctions including desmosomes, subapical tight junctions, adherens junctions, and scattered gap junctions. Once epithelial cells are damaged, the epithelial cell-cell junctions are dissolved, and the epithelial cells lose their apical-basal polarity and acquire a front-rear polarity. In addition, the cytoskeletal architecture is reorganized, and the expression of E-cadherin is replaced by the expression of N-cadherin, which contributes to cell motility and invasiveness. Then, the basement membrane is dissolved. During embryonic genesis, epithelia and mesenchymal cells mutually transform via EMT and MET, which is characterized as type I EMT and is critical for embryonic development and organ formation. In type II EMT, the mesenchymal-like cells are then transformed into myofibroblasts, which produce excessive collagen leading to fibrosis. In type III EMT, mesenchymal-like cells migrate along with the circulatory system to a secondary location, where the migratory cells form a secondary tumor via MET. The green pane indicates a common process in the three types of EMT that can be targeted to treat both fibrosis and tumor. EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition [Color figure can be viewed at wileyonlinelibrary.com]

Metformin is a first-line drug for treating type II diabetes mellitus that has shown a therapeutic effect on many cancers. Further study revealed that metformin increased the expression of E-cadherin, miR-200a, miR-200c, and miR-429 and decreased the expression of miR-34a, vimentin, Snail1 and ZEB1 in transforming growth factor- β (TGF- β)-induced EMT in the colorectal cancer cell lines SW480 and HCT-116 (Table 1).⁵⁷ In addition, some compounds derived from natural products have also shown significant intervention in fibrosis and tumors by targeting Snail (Table 1). Toosendanin, a triterpenoid isolated from *Melia toosendan* Sieb. et Zucc (Meliaceae), is

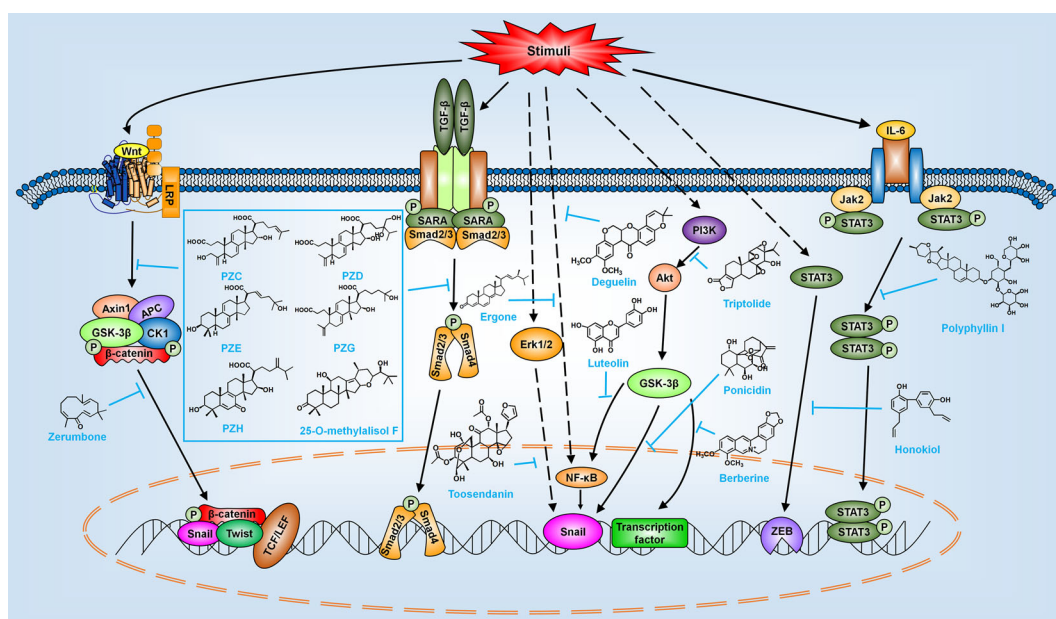


FIGURE 2 The molecular mechanisms of EMT and compounds from natural products that suppress EMT. EMT mediators, including the transcription factors Snail, ZEB and STAT3 and the signaling pathways NF- κ B, Wnt/ β -catenin, TGF- β 1/Smad, and PI3K/Akt, are presented. Small molecules used for treatment and their targets are presented. Akt, RAC- α serine/threonine-protein kinase; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; GSK3 β , glycogen synthase kinase-3 β ; JAK2, Janus kinase 2; IL-6, interleukin-6; NF- κ B, nuclear factor κ B; PI3K, phosphatidylinositol 3-kinase; STAT3, signal transducer and activator of transcription 3; ZEB, zinc-finger E-box-binding [Color figure can be viewed at wileyonlinelibrary.com]

used to prevent and control agricultural pests.⁹⁷ Recently, it was reported that toosendanin significantly inhibited TGF- β 1-induced EMT in lung cancer cells via the extracellular signal-regulated kinase (ERK)/Snail pathway and suppressed EMT and tumor growth in pancreatic cancer by deactivating the RAC- α serine/threonine-protein kinase (Akt)/mechanistic target of rapamycin (mTOR) pathway (Figure 2), which suggests that toosendanin is a promising pharmacological agent for the treatment of cancer.^{22,23} A recent study revealed that neferine enhanced oxaliplatin sensitivity by inhibiting EMT via the Snail pathway.¹⁹ In addition, ponocidin is a major diterpenoid compound extracted from *Rabdosia rubescens* (Hemsl.) Hara that exhibited a therapeutic effect on TNF- α -induced EMT and the metastasis of colorectal cancer by targeting the Akt/glycogen synthase kinase-3 β (GSK3 β)/Snail pathway³¹ (Figure 2). Moreover, ferulic acid is a bioactive component derived from *Ligusticum chuanxiong* Hort that suppressed EMT induced by TGF- β 1 via inhibiting the Smad/integrin-linked kinase/Snail signaling pathway in a renal proximal tubular epithelial cell line (NRK-52E), suggesting that ferulic acid might be potent fibrosis antagonist.⁹⁸

2.1.2 | ZEB transcription factors

The two ZEB family members, ZEB1 and ZEB2, are transcriptional inhibitors that are involved in cell proliferation, migration, invasion, and apoptosis. Extensive studies have confirmed that ZEB1 is upregulated in the EMT and plays a key role in the development of tumors and fibrosis.^{99,100} It was reported that the Np63-miR-205 axis increased epithelial marker gene expression and decreased mesenchymal marker gene expression in oral squamous cell carcinoma by downregulating ZEB1 and ZEB2.¹⁰¹ Moreover, the heterogeneous expression of ZEB1 induced by EMT played an important role in metastasis through the regulation of miR-200c.¹⁰² In addition, miR-302a-3p exerted a protective role via inhibiting ZEB1 and EMT in diabetic kidney disease.¹⁰³ These results suggest that

TABLE 1 Anti-EMT effects of small molecules

Compound	Compound type	Source	Disease	Signaling pathways	References
Toosendanin	Terpene	<i>Melia toosendan</i> Sieb. et Zucc (Meliaceae)	Lung cancer cells, pancreatic cancer	ERK/Snail, Akt/mTOR	22,23
Betulinic acid	Terpene	<i>Betula</i> spp.	Melanoma	AMPK	24
Codonolactone	Terpene	<i>Atractylodes Lancea</i> (Thunb.) DC.	Breast cancer cells	TGF- β	25
Zerumbone	Terpene	<i>Zingiber Zerumbet</i> (L.) Smith	Colorectal cancer cells	β -Catenin	26
Triptolide	Terpene	<i>Tripterygium wilfordii</i> Hook F	Diabetic kidney disease, IPF	PI3K/Akt, TGF- β	27,28
Poricoic acid ZC	Terpene	<i>Poria cocos</i> (Polyporaceae)	Renal fibrosis	Wnt/ β -catenin, TGF- β 1	29
Poricoic acid ZD					
Poricoic acid ZE					
Poricoic acid ZG	Terpene	<i>Poria cocos</i> (Polyporaceae)	Renal fibrosis	Wnt/ β -catenin, TGF- β 1	29
Poricoic acid ZH					
25-O-methylalisol F	Terpene	<i>Alisma orientale</i> (Sam.) Juzep	Renal fibrosis	Wnt/ β -catenin, TGF- β 1	30
Alisol B 23-acetate	Terpene	<i>Alisma orientale</i> (Sam.) Juzep	Renal fibrosis	Wnt/ β -catenin	30
Ponicidin	Terpene	<i>Rabdosia rubescens</i> (Hemsl.) Hara	Colorectal cancer cells	Akt/GSK3 β /Snail	31
Tanshinone IIA	Terpene	<i>Salvia miltiorrhiza</i>	Bladder cancer cells, lung fibrosis	STAT3-CCL2, TGF- β /Smad	32,33
Simvastatin	Terpene		Ec9706-R cells	PTEN/PI3K/Akt	34
Oridonin	Terpene	<i>Rabdosia rubescens</i> (Hemsl.) Hara	Osteosarcoma	TGF- β 1/Smad2/3	35
Icaritin	Flavonoid	<i>Epimedium genus</i>	Glioblastoma cells	PTEN/Akt/HIF-1 α ,	36
Luteolin	Flavonoid	<i>Salvia tomentosa</i>	Gastric cancer, lung cancer cells, lung fibrosis	Notch, PI3K/Akt-NF- κ B-Snail	37,38
Silibinin	Flavonoid	<i>Silybum marianum</i>	Bladder cancer	β -Catenin/ZEB1	39
Rhamnetin and Cirsiliol	Flavonoid	Cloves and berries, <i>Cirsium lineare</i> (Thunb.) Sch.-Bip.	Non-small-cell lung cancer cells	Notch1	40
Nobiletin	Flavonoid	<i>Citrus depressa</i>	Human non-small-cell lung cancer cells	Notch1, TGF- β 1/Smad	41,42
Deguelin	Flavonoid	<i>Derris trifoliata</i>	Pancreatic cancer cells	NF- κ B	43
Quercetin	Flavonoid	Fruits, vegetables and beverages	Pancreatic cancer cells, renal fibrosis	STAT3, miR-21	44,45

(Continues)

TABLE 1 (Continued)

Compound	Compound type	Source	Disease	Signaling pathways	References
Isoviolanthin	Flavonoid	<i>Dendrobium officinale</i>	Hepatocellular carcinoma cells	TGF- β 1/Smad, PI3K/Akt/mTOR	46
3,6-Dihydroxyflavone	Flavonoid	Vegetables and fruits	Breast cancer cells	Notch	47
⁵⁸ Berberine	Alkaloid	<i>Berberis vulgaris</i>	Diabetic nephropathy, melanomas	PI3K/Akt and RAR α /RAR β , Notch/Snail	48,49
Nicotine	Alkaloid	<i>Nicotiana rustica</i> L.	Non-small-cell lung cancer cells	MIR-99b and miR-192	50
Sophocarpine	Alkaloid	<i>Sophora alopecuroides</i> L.	Head and neck cancer, hepatocellular carcinoma	MIR-21, Akt/GSK3 β / β -catenin	51,52
Evodiamine	Alkaloid	<i>Evodia rutaecarpa</i> (Juss.) Benth.	Rat renal proximal tubular epithelial cells	PPAR γ and Smad	53
Caffeine	Alkaloid	Coffee	Hela cells, liver fibrosis	Serine/arginine-rich splicing factor 3, Snail and Nrf2	54,55
Neferine	Alkaloid	<i>Nelumbo nucifera</i> Gaertn.	Hepatocellular carcinoma	Snail1	56
Metformin	Alkaloid		Colorectal cancer cell lines SW480 and HCT-116	Snail1	57
Decitabine	Alkaloid		Non-small-cell lung cancer PC9 cells	MIR-200/ZEB	58
Sepantronium bromide	Alkaloid		Glioblastoma	STAT3	59
Trichostatin A	Alkaloid		Lung fibrosis	Akt	60
Ubenimex	Alkaloid		Renal cell carcinoma	Akt	61
Galunisertib	Alkaloid		Human hepatocellular carcinoma cell lines	TGF β RI	62
GW788388	Alkaloid		Renal fibrosis	TGF β RI	63
Oxymatrine	Alkaloid		NRK-52E cells	TGF- β 1/Smad	64
FH355	Alkaloid		Radioresistant esophageal cancer cell line	Wnt/ β -catenin	65
DAPT	Alkaloid		Oral squamous cell carcinoma cell lines	Notch	66
RO4929097	Alkaloid		Cervical cancer cells	Notch	67
Losartan	Alkaloid		Hyperglycemia	RAS	68

(Continues)

TABLE 1 (Continued)

Compound	Compound type	Source	Disease	Signaling pathways	References
Curcumin	Phenol	<i>Cnidium monnieri</i> (L.) Cuss.	Pancreatic cancer cells, breast cancer cells, intestinal fibrosis, bladder cancer	Wnt/ β -catenin, c-Met/PI3K/Akt/mTOR, PPAR γ , NF- κ B, Snail, miR-34a	69-72
Resveratrol	Phenol	<i>Vaccinium</i> shrubs	HCT-116 colorectal cancer cells, gastric cancer, renal fibrosis, lung fibrosis	PTEN/Akt, miR-200c, TGF- β , p38-MAPK, TGF- β	73-76
Hispolon	Phenol	<i>Phellinus linteus</i> (Berkeley and Curtis) Teng	Human epithelial cancer cells	TGF- β Snail/Twist	77
Honokiol	Phenol	<i>Magnolia grandiflora</i> L.	Breast cancer, renal cancer cells	STAT3/ZEB1/E-cadherin, LKB1/miR-34a, miR-141/ZEB2	78-80
Ergone	Steride	<i>Polyporus umbellatus</i> (Pers.) Fries	Renal fibrosis	Wnt/ β -catenin	81
Polyphyllin I	Steride	<i>Paris polyphylla</i>	Prostate cancer, lung cancer cells	IL-6/STAT3, CIP2A/PP2A/ERK, CIP2A/PP2A/Akt	82,83
Telocinobufagin	Steride	Chan Su (<i>Venenum Bufonis</i>)	Breast cancer cells	PI3K/Akt/ERK/Snail	84
Thymoquinone	Quinone	<i>Nigella sativa</i>	Renal cell carcinoma, cervical cancer cells, prostate cancer cells, gastric cancer cells	Twist1 and ZEB1, LKB1/AMPK, TGF- β /Smad2/3, PI3K/Akt/mTOR	85-88
α -Mangostin	Xanthon	<i>Garcinia mangostana</i> L.	Pancreatic cancer cells	PI3K/Akt	89
Pterostilbene	Stilbenoid	Blueberries	Breast cancer stem cells, renal fibrosis	NF- κ B/miR-488, TGF- β 1	90,91
Osthole	Coumarin	<i>Cnidium monnieri</i> (L.) Cuss	Lung cancer A549 cells, prostate cancer	NF- κ B/Snail, miR-23a-3p	92,93
Vitamin D			Human bronchial epithelial cells	TGF- β 1	94
Salinomycin	Polyketide		Epithelial ovarian cancer cells	Wnt/ β -catenin	95
Emodin	Anthraquinone	<i>Polygonum cuspidatum</i>	Alveolar epithelial cells	Notch	96

Abbreviations: Akt, RAC- α serine/threonine-protein kinase; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; CCL2, chemokine (C-C motif) ligand 2; ERK, extracellular signal-regulated kinase; HIF-1 α , hypoxia-inducible factor 1 α ; IL-6, interleukin-6; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PPAR, peroxisome proliferator-activated receptor; PTEN, phosphatase and tensin homologue; RAR, retinoic acid receptor; STAT3, signal transducer and activator of transcription 3.

various mediators contribute to EMT via the ZEB signaling pathway, suggesting that ZEB is a promising target for the treatment of fibrosis and tumors.

Decitabine is a drug used to treat myelodysplastic syndromes that inhibited EMT by regulating the miR-200/ZEB signaling pathway in non-small-cell lung cancer PC9 cells.⁵⁸ In addition, a phase Ib/II clinical trial revealed that low-dose decitabine enhanced the efficacy of immunotherapy in patients with drug-resistant relapsed/refractory alimentary tract cancer, making it an attractive therapy for cancers.¹⁰⁴

Silibinin, a bioactive component from *Silybum marianum* (L.) Gaertn., exhibited anticancer properties in multiple types of cancer, such as bladder and lung cancer (Table 1). Recent studies revealed that silibinin reversed EMT by inhibiting the expression of ZEB1, vimentin, and MMP-2 as well as the transactivation of β -catenin in bladder cancer metastasis.³⁹ Furthermore, the combined treatment of silibinin with trichostatin A (an inhibitor of histone deacetylases) or decitabine suppressed EMT in non-small-cell lung cancer.¹⁰⁵ These studies suggest that silibinin is an important candidate anticancer drug. Honokiol was extracted from the seed cones of *Magnolia grandiflora* L. and showed a therapeutic effect on various cancers. Honokiol effectively inhibited EMT in breast cancer through the STAT3/ZEB1/E-cadherin axis (Figure 2) and reversed EMT in renal cell carcinoma via miR-141/ZEB2 (Table 1).^{78,79}

2.1.3 | STAT3

STAT3, a member of the STAT protein family, can be phosphorylated as a transcription factor and plays a key role in various cellular processes, including cell growth, apoptosis, and differentiation. Hypoxia is a key mediator that induces EMT during tumor initiation and metastasis, and STAT3 promotes HIF-1 α expression to induce EMT by binding to the promoter of HIF-1 α . In addition, STAT3 was identified as a positive regulator that aggravated TGF- β 1-induced EMT.¹⁰⁶ In particular, the JAK2/STAT3 signaling pathway had a significant effect on the EMT in multiple cancers.^{107,108} In addition, STAT3 cooperated with other transcription factors promoting EMT, such as Twist and ZEB1.¹⁰⁹ For example, the expression of p-STAT3 (Tyr-705) and ZEB1 was positively associated with metastasis, and they cooperatively enhanced EMT in colorectal carcinoma.¹¹⁰ Moreover, STAT3 was upregulated in TGF- β 1-induced EMT during renal fibrosis, implying that STAT3 is an innovative target for the prevention of fibrosis.¹¹¹ Furthermore, there are many mediators that induce EMT through the activation of STAT3, such as Pin1, HOXB8, miR-30d, and IL-6.^{112–115}

Sepantronium bromide is an inhibitor of survivin that exhibits anticancer properties in multiple cancer types. A recent study revealed that sepantronium bromide reduced the invasion of glioblastoma induced by radiation and reversed EMT by targeting STAT3.⁵⁹

Tanshinone IIA is a major bioactive component from the famous medical herb *Salvia miltiorrhiza* that was reported to attenuate the proliferation of bladder cancer cells (Table 1). Further study revealed that tanshinone IIA suppressed EMT in bladder cancer cells via the modulation of the STAT3-CCl2 signaling pathway.³² In addition, tanshinone IIA blocked EMT by regulating the TGF- β /Smad pathway in peritoneal fibrosis.¹¹⁶ From these data, it was suggested that compounds that target EMT might have both antifibrotic and anticancer properties. In addition, polyphyllin I, a steroidal saponin derived from *Paris polyphylla*, has shown anti-inflammatory and anticancer properties. It was suggested that polyphyllin I, which reversed EMT by modulating the IL-6/STAT3 pathway, served as a novel solution to conquer EGFR-TKI resistance in non-small-cell lung cancer⁸² (Figure 2). Therefore, combined treatment with polyphyllin I and erlotinib is a promising therapy for lung cancer patients to strengthen drug efficacy and reduce drug resistance.⁸² The other compound, quercetin, is a flavonoid widely distributed in fruits, vegetables, and beverages that shows antioxidative, anti-inflammatory, and anticancer properties. Quercetin reversed IL-6-induced EMT in pancreatic cancer cells through STAT3.⁴⁴ Collectively, the data indicate that the use of compounds targeting STAT3 might be an effective approach for curing fibrosis and cancer.

2.2 | Targeting signaling pathways against EMT by small molecules

Many signaling pathways, such as the TGF- β 1, nuclear factor- κ B (NF- κ B), Wnt, Akt, peroxisome proliferator-activated receptor (PPAR), and Notch pathways, and the renin-angiotensin system (RAS) contribute to the EMT. Targeting these signaling pathways may be effective for the treatment of fibrosis and tumors, and many small molecules that target these signaling pathways reverse EMT in fibrosis and tumors.

2.2.1 | TGF- β 1 signaling pathway

TGF- β 1 plays a crucial role in various cellular functions, including cell growth, proliferation, differentiation, and apoptosis, and is considered a key mediator in EMT during the processes of tumor formation and fibrosis.¹¹⁷ Many components contribute to EMT through the TGF- β 1 signaling pathway, which indicates that the inhibition of the TGF- β 1 signaling pathway may be effective in the treatment of cancer and fibrosis. Several excellent reviews have discussed the role of the TGF- β 1 signaling pathway in tumors and fibrosis well.^{117,118} Here, we present several important small molecules that suppress EMT in tumors and fibrosis by targeting the TGF- β 1 signaling pathway (Table 1).

Galunisertib, also known as LY2109761, is a TGF- β receptor kinase inhibitor that specifically downregulated the phosphorylation of Smad2 and upregulated E-cadherin expression in cultured human hepatocellular carcinoma cell lines, implying that it could suppress the EMT.¹¹⁹ Galunisertib is now in ongoing clinical trials in patients with glioblastoma, pancreatic cancer, and hepatocellular carcinoma.⁶² Nobiletin is a flavonoid compound isolated from *Citrus depressa* that suppressed EMT by antagonizing the TGF- β 1/Smad signaling pathway in human non-small-cell lung cancer cells.⁴² In addition, oridonin is a diterpenoid from *Rabdosia rubescens* (Hemsl.) Hara that inhibited EMT via blocking TGF- β 1/Smad2/3 in osteosarcoma.³⁵ Moreover, GW788388 is a novel inhibitor of TGF- β type I receptor that inhibited TGF- β -induced EMT and fibrogenesis in db/db mice that showed significant diabetic nephropathy.⁶³ Furthermore, oxymatrine, a bioactive alkaloid from *Sophora japonica* L., alleviated EMT induced by high glucose through inhibiting the TGF- β 1/Smad signaling pathway in NRK-52E cells, indicating that oxymatrine might be a therapeutic agent for diabetic nephropathy.⁶⁴ Isoviolanthin, a flavonoid isolated from *Dendrobium officinale* Kimura et Migo, suppressed TGF- β 1-induced EMT through inhibiting the TGF- β 1/Smad and phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signaling pathways in hepatocellular carcinoma cells.⁴⁶ In addition, vitamin D, a well-known inhibitor of EMT, inhibited EMT by negatively regulating the TGF- β 1 signaling pathway in human bronchial epithelial cells, and MART-10 (a vitamin D analogue) suppressed metastasis via downregulating EMT in pancreatic cancer cells.^{94,120}

2.2.2 | NF- κ B signaling pathway

The NF- κ B signaling pathway is widely involved in multiple cellular activities, such as cell proliferation, apoptosis, invasion, and inflammation. NF- κ B plays a vital role in the inflammation of tissue fibrosis, and inhibiting NF- κ B activity reduced inflammation and enhanced recovery from CCl₄-induced liver fibrosis.¹²¹ In addition, NF- κ B contributed to inflammation, apoptosis, growth, migration, and invasion of cancer cells.^{122,123} Recently, it was found that the mediator of RNA polymerase II transcription, subunit 28 (MED28) modulated EMT through NF- κ B in human breast cancer cells, which suggests that the NF- κ B signaling pathway also plays a key role in the process of EMT.¹²⁴ Therefore, targeting the NF- κ B signaling pathway may be a good choice to treat fibrosis and tumors.

Osthole, a dominant component in *Cnidium monnieri* (L.) Cuss., exhibited various biological activities including neuroprotective, osteogenic, cardiovascular protective, immunomodulatory, hepatoprotective, and antimicrobial effects. Osthole was found to block TGF- β 1-induced EMT, adhesion, migration, and invasion by the inactivation of the NF- κ B/Snail pathways in A549 cells (Table 1).⁹² In addition, osthole also attenuated insulin-like growth factor-1-induced EMT by the PI3K/Akt pathway and inhibited hepatocyte growth factor-induced EMT via the c-Met/Akt/mTOR pathway in human brain cancer cells.¹²⁵ Pterostilbene is a stilbene containing in blueberries that effectively

blocked the EMT in breast cancer stem cells by the NF- κ B/miR-488 circuit.⁹⁰ Moreover, pterostilbene negatively regulated EMT and inhibited triple-negative breast cancer metastasis via inducing the expression of miR-205.¹²⁶

The sclerotia of *Polyporus umbellatus* (Pers.) Fries is widely used to promote urination and prevent dampness.¹²⁷ Our previous studies systematically demonstrated that ergosta-4,6,8(14),22-tetraen-3-one (ergone) isolated from *Polyporus umbellatus* (Pers.) Fries showed significant antitumor, diuretic, and renoprotective effects.¹²⁸⁻¹³⁵ Our recent study demonstrated that ergone inhibited NF- κ B signaling and α -SMA expression in 5/6 nephrectomised and unilateral ureteral obstruction rats^{136,137} (Figure 2 and Table 1).

2.2.3 | Wnt signaling pathway

The Wnt signaling pathway is an evolutionarily conserved developmental signaling cascade that plays a critical role in regulating organ development and tissue homeostasis. Leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5) is a novel functional marker in glioma stem cells that promotes EMT by activating the Wnt/ β -catenin signaling pathway.¹³⁸ Sry-like high-mobility group box 8 regulated cancer stem-like properties and cisplatin-induced EMT by the Wnt/ β -catenin signaling pathway in tongue squamous cell carcinoma.¹³⁹ In addition, bone marrow mesenchymal stromal cells suppressed EMT by inhibiting the Wnt/ β -catenin signaling pathway in silica-induced pulmonary fibrosis.¹⁴⁰ Our previous study showed the activation of the canonical Wnt/ β -catenin signaling pathway accompanied by the upregulation of proinflammatory and pro-oxidative protein expression in the NF- κ B signaling pathway and downregulation of the anti-inflammatory Nrf2 signaling pathway in patients with chronic kidney disease compared with the Nrf2 signaling pathway in healthy controls.¹⁴¹

Many compounds inhibit the Wnt signaling pathway, and these compounds may suppress EMT in cancer and fibrosis (Table 1).¹⁴² FH535, a β -catenin/Tcf inhibitor, not only increased radio-sensitivity but also suppressed EMT in the radioresistant KYSE-150R esophageal cancer cell line, which indicated that inhibitors of the Wnt signaling pathway might be effective anticancer agents with the potential to be anticancer drugs.⁶⁵ In addition, it was reported that FH535 alleviated multiple types of cancer, including colorectal cancer, gastric cancer, and hepatocellular carcinoma.¹⁴³⁻¹⁴⁵ Isoquercitrin, a bioactive flavonoid from *Bidens bipinnata* L., inhibited the Wnt/ β -catenin signaling pathway and hepatocyte growth factor/scatter factor-induced EMT in NBT-II cells.¹⁴⁶ In addition, salinomycin was previously used as an antibiotic and also showed significant anticancer activity by suppressing EMT.^{95,147,148} Salinomycin-inhibited EMT by suppressing the Wnt/ β -catenin signaling pathway in epithelial ovarian cancer cells, indicating that small molecules targeting the Wnt/ β -catenin signaling pathway might have anticancer properties by reversing EMT.⁹⁵ *Poria cocos* (Polyporaceae) is a well-known fungus that exhibits an effective therapeutic effect to improve kidney function in clinic.^{149,150} Our previous studies have confirmed that extracts of the surface layer of *Poria cocos* show remarkable antihyperlipidemic, diuretic, and renoprotective effects.¹⁵¹⁻¹⁵⁸ Recently, our group isolated more than 90 triterpenoid compounds from the surface layer of *Poria cocos*, some of which exhibited significant antifibrotic properties.¹⁵⁹⁻¹⁶¹ New triterpenoids, including poricoic acid ZC, poricoic acid ZD, and poricoic acid ZE, significantly downregulated the expression of Wnt1, active β -catenin, Snail, Twist, MMP-7, PAI-1, and FSP1 in HK-2 cells induced by TGF- β 1 and angiotensin II and mice with unilateral ureteral occlusion²⁹ (Figure 2 and Table 1). Moreover, new triterpenoids, including poricoic acid ZG and poricoic acid ZH, improved renal fibrosis by targeting the phosphorylation of Smad3 signaling and the Wnt/ β -catenin signaling pathway¹⁶² (Figure 2 and Table 1).

Alismatis rhizome (AR), the dried rhizome of *Alisma orientale* (Sam.) Juzep, exhibited diuretic, antihyperlipidemic, and renoprotective effects¹⁶³ that were also confirmed by our previous studies.¹⁶⁴⁻¹⁶⁷ Our recent study demonstrated that triterpenoid was the main component of AR,³⁰ and further study showed that the novel tetracyclic triterpenoid 25-O-methylalisol F inhibited EMT by suppressing the Wnt/ β -catenin signaling pathway as well as the phosphorylation of Smad3 signaling in both NRK-52E and NRK-49F cells³⁰ (Figure 2 and Table 1). Additionally, it was also observed that ergone inhibited extracellular matrix accumulation in HK-2 cells and attenuated podocyte injury through inhibiting the activation of the Wnt/ β -catenin signaling pathway induced by

angiotensin II.⁸¹ Taken together, these data indicate that tetracyclic triterpenoid and steroid compounds show significant antifibrotic properties in renal fibrosis.

2.2.4 | Akt signaling pathway

Akt (also known as protein kinase B or Rac) is a serine/threonine-specific protein kinase that plays a key role in various cellular activities. Many cellular signals are transduced through the Akt signaling pathway, and Akt is involved in EMT in cooperation with other proteins. For example, tripartite motif-containing 14 is an oncogene that regulated EMT and the metastasis of human gastric cancer by activating Akt signaling.¹⁶⁸ M3 muscarinic acetylcholine receptors regulated EMT, perineural invasion, and metastasis in cholangiocarcinoma via the Akt pathway.¹⁶⁹ Canopy homologue 2 promoted EMT via activating the Akt/GSK3 pathway in non-small-cell lung cancer.¹⁷⁰ The Akt signaling pathway mediated cigarette-induced EMT in lung cancer.¹⁷¹ In addition, Akt also promoted EMT cooperation with miRNAs. MiR-944 inhibited EMT and the metastasis of gastric cancer by the metastasis-associated in colon cancer 1 (MACC1)/Met/Akt signaling pathway.¹⁷² MiR-1296 inhibited EMT and the metastasis of hepatocellular carcinoma via the serine/threonine-protein kinase 1/PI3K/Akt signaling pathway.¹⁷³ Taken together, these data suggest that Akt plays a key role in EMT cellular signal transduction and that targeting Akt might be an effective approach to treat fibrosis and tumors (Table 1).

Simvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor that was originally used to treat cardiovascular diseases. Recently, it was reported that simvastatin had a therapeutic effect in several cancers. The administration of simvastatin suppressed EMT through the phosphatase and tensin homologue (PTEN)/PI3K/Akt pathway in EC9706-R cells, suggesting a new therapeutic function for simvastatin in cancers.³⁴ Trichostatin A, a histone deacetylase inhibitor, is an antifungal antibiotic. In addition to its antibiotic properties, trichostatin A alleviated EMT in bleomycin-induced lung injury in mice via inhibiting the Akt signaling pathway.⁶⁰

Ubenimex inhibits multiple proteases, including arginyl aminopeptidase, leukotriene A₄ hydrolase, alanyl aminopeptidase, and leucyl/cysteinyl aminopeptidase, a membrane dipeptidase used to treat acute myelocytic leukemia and lymphedema. Ubenimex alleviated acquired sorafenib (a first-line anticancer drug) resistance in renal cell carcinoma via suppressing the Akt pathway.⁶¹

Luteolin is widely distributed in plants and has shown anti inflammatory, antioxidant, antimicrobial, and antitumor properties. Luteolin attenuated TGF- β 1-induced EMT by mediating the PI3K/Akt/NF- κ B-Snail pathway in lung cancer cells³⁷ (Figure 2). In addition, luteolin attenuated the progression of gastric cancer by reversing EMT via the Notch signaling pathway.³⁸ Moreover, luteolin also suppressed the metastasis of triple-negative breast cancer via blocking EMT by the downregulation of β -catenin.¹⁷⁴ Furthermore, luteolin suppressed EMT by downregulating the expression of cyclic AMP-responsive element binding protein 1¹⁷⁵ in colorectal cancer cells.¹⁷⁶ Collectively, luteolin showed therapeutic effects in both tissue fibrosis and tumors through various signaling pathways and might be a promising candidate to treat fibrosis and tumors.

α -Mangostin derived from the pericarp of the mangosteen fruit has been shown to have various cellular functions, such as arresting the cell cycle, inhibiting cell viability, inducing apoptosis, and differentiation, reducing inflammation and decreasing adhesion. α -Mangostin suppressed viability and EMT by downregulating the PI3K/Akt pathway in pancreatic cancer.⁸⁹ Icaritin, a hydrolytic product of icariin that is isolated from members of the *Epimedium* genus, induced the trans-differentiation of embryonic stem cells into cardiomyocytes, prevented steroid-associated osteonecrosis and stimulated neuronal differentiation.³⁶ Icaritin inhibited invasion and EMT via targeting the PTEN/Akt/HIF-1 α signaling pathway.³⁶

2.2.5 | PPAR γ signaling pathway

PPAR belongs to the nuclear hormone receptor superfamily and consists of three isoforms including PPAR α , PPAR β/δ , and PPAR γ . PPAR played essential roles in the regulation of cellular differentiation, development,

metabolism, and tumorigenesis; in particular, PPAR γ exerted a protective role in the development of fibrosis and tumors. A recent study revealed that the activation of PPAR γ attenuated cardiac fibrosis, which was mediated by the downregulation of EMT and the TGF- β /ERK pathway.¹⁷⁷ In addition, the overexpression of miR-130b promoted EMT in glioma cells and human hepatocellular carcinoma, and PPAR γ was identified as a functional target of miR-130b, which was inversely correlated with PPAR γ .¹⁷⁸ Moreover, it was reported that the PPAR γ agonist pioglitazone suppressed fibrotic changes in primary monkey retinal pigment epithelial cells by inhibiting the TGF- β signaling pathway.¹⁷⁹ Collectively, these results suggest that PPAR γ might be a therapeutic target against fibrosis and tumors (Table 1).

Evodiamine from *Evodia rutaecarpa* (Juss.) Benth. exerts anti inflammatory, antiobesity, antianxiety, antiallergic, and anticancer effects. Evodiamine suppressed TGF- β 1-induced EMT in NRK-52E cells via the PPAR γ signaling pathway.⁵³ In addition, curcumin is an active component of *Curcuma longa* L. that exhibits antioxidant, antibacterial, antifungal, antiviral, anti inflammatory, antiproliferative, and anticarcinogenic properties. Curcumin had an antifibrotic effect in intestinal fibrosis and prevented the EMT by the PPAR γ signaling pathway.⁶⁹

2.2.6 | Notch signaling pathway

As a highly conserved cell signaling system, the Notch signaling pathway is widely involved in cell proliferation and differentiation during embryonic and adult development. Extensive studies have demonstrated that the Notch signaling pathway is also critical for EMT in tumorigenesis and fibrogenesis. The overexpression of Notch1-induced EMT in PC-3 cells, and claudin-1 contributed to EMT by the Notch signaling pathway in human bronchial epithelial cells.^{180,181} In addition, Notch and TGF- β 1 generated a reciprocal positive regulatory loop and cooperatively regulated EMT in epithelial ovarian cancer cells, which provided new insight into the mechanism of EMT.¹⁸² Moreover, miR-34a downregulation induced by hypoxia enhanced EMT via the Notch signaling pathway in tubular epithelial cells, which indicated that the Notch signaling pathway is critical for EMT during fibrosis.⁶⁶ These cases suggest that a targeted intervention in the Notch signaling pathway might be an effective strategy to treat cancer and fibrosis.

DAPT, a γ -secretase inhibitor, decreased the expression of Snail and vimentin and increased E-cadherin expression in two oral squamous cell carcinoma cell lines, Tca8113 and CAL27, indicating that the targeted inhibition of the Notch signaling pathway might be a new therapeutic strategy to treat cancer.^{183,184} Another γ -secretase inhibitor, RO4929097, not only inhibited EMT, invasion, and metastasis in cervical cancer HeLa and CaSki cells but also exerted significant therapeutic effects in patients with recurrent malignant glioma, cervical and colon cancer and advanced solid tumors in clinical trials.^{67,185,186} 3,6-Dihydroxyflavone is ubiquitous in vegetables and fruits and blocks EMT in breast cancer cells through suppressing the Notch signaling pathway.⁴⁷ Moreover, luteolin inhibited EMT in gastric cancer by the Notch signaling pathway.³⁸ In addition, emodin is a main bioactive component of *Polygonum cuspidatum* that suppressed EMT in alveolar epithelial cells via the Notch signaling pathway. Therefore, it is a promising prospect in treating pulmonary fibrosis.⁹⁶ Furthermore, berberine was isolated from *Berberis vulgaris* and reversed EMT by blocking the Notch/Snail signaling pathway in mice with diabetic nephropathy.⁴⁸

2.2.7 | RAS signaling pathway

The RAS signaling pathway not only regulates blood pressure and fluid balance but also is involved in many kinds of diseases, including cancer and fibrosis. Recently, emerging evidence has suggested that the RAS signaling pathway plays a key role in EMT during fibrosis and tumorigenesis. Angiotensin II promoted EMT by the interaction between hematopoietic stem cells and the stromal cell-derived factor-1/CXR4 axis in intrahepatic cholangiocarcinoma.¹⁸⁷ In addition, the overexpression of angiotensin II type 1 receptor induced EMT and promoted tumorigenesis in human breast cancer cells, and the silencing of angiotensin II type 1 receptor suppressed EMT that was induced by high glucose through inactivating the mTOR/p70s6k signaling pathway in the human proximal tubular epithelial HK-2

cell line.^{188,189} Based on these results, it was suggested that suppressing RAS might be an effective therapy to treat cancer and fibrosis.

Losartan is an AT1R antagonist that improved renal fibrosis by suppressing EMT in rats with hyperglycemia.⁶⁸ Although many RAS inhibitors showed beneficial effects in tumors and fibrosis, few were reported to inhibit EMT in the treatment of cancer and fibrosis.^{190,191}

2.3 | Targeting miRNA signaling pathways by small molecules

MiRNAs are endogenous small noncoding RNAs (19-25 nucleotides) that bind the 3'-untranslated region of messenger RNAs to regulate gene expression. Recently, many miRNAs have been found to promote or suppress EMT in fibrosis and tumors. For example, miRNA-497/Wnt3a/c-Jun regulated growth and EMT, and miR-497 served as a tumor suppressor in glioma cells.¹⁹² Moreover, miR-205 inhibited tumor growth, invasion, and EMT via targeting semaphorin 4C in hepatocellular carcinoma.¹⁹³ Furthermore, the upregulation of miR-183-5p induced apoptosis and inhibited EMT, proliferation, invasion, and migration by the downregulation of ezrin in human endometrial cancer cells.¹⁹⁴ Collectively, EMT is inhibited by many miRNAs, including miR-145, miR-497, miR-145-5p, miR-138, miR-200a, miR-200b, miR-655, miR-30-5p, and miR-32.¹⁹⁵⁻²⁰¹ In addition, EMT is also promoted by many miRNAs, including miR-221, miR-222, miR-214-3p, and miR-181a.²⁰²⁻²⁰⁴

The flavonoids rhamnetin from cloves, berries and cirsiolol from *Cirsium lineare* (Thunb.) Sch.-Bip. showed anti inflammatory and antitumor properties. Both rhamnetin and cirsiolol induced radio-sensitization and inhibited EMT by miR-34a/Notch1 signaling in non-small-cell lung cancer cells.⁴⁰ Quercetin alleviated TGF- β 1-induced fibrosis in HK-2 cells via downregulating miR-21 expression and upregulating PTEN and TIMP metalloproteinase inhibitor 3 (TIMP3) expression.⁴⁵ Sophocarpine from *Sophora alopecuroides* L. inhibited tumor progression and reversed EMT by targeting miR-21 in head and neck cancer.⁵¹ In addition, sophocarpine exerted a profound antitumor effect through inhibiting EMT induced by TGF- β .⁵² Zerumbone from *Zingiber zerumbet* (L.) Smith exhibited anti-inflammatory and anticancer properties. Recently, it was reported that zerumbone inhibited the β -catenin pathway via miR-200c to block EMT and cancer stem cells.²⁶ In addition, nicotine upregulated FGFR3 and RB1 and promoted EMT by the downregulation of miR-99b and miR-192 in non-small-cell lung cancer cells.⁵⁰ Moreover, osthole alleviated EMT-mediated metastasis by inhibiting miR-23a-3p.⁹³ Furthermore, resveratrol inhibited proliferation, invasion, and EMT via the upregulation of miR-200c in HCT-116 colorectal cancer cells.⁷³

2.4 | Targeting RNA splicing protein signaling pathways by small molecules

RNA-binding proteins such as RNA-binding Fox protein 2 (Rbfox2), epithelial splicing regulatory protein 1 (ESRP1), and ESRP2 control the splicing of many gene transcripts and splice nascent RNAs to functionally and structurally different miRNAs to regulate the process of EMT. For example, bleomycin inhibited ESRP1 expression, leading to the increased alternative splicing of FGFR2 to its mesenchymal isoform IIIc, which induced EMT in lung fibrosis.²⁰⁵ In addition, overexpressed ESRP1 contributed to EMT in ovarian cancer, inducing a cell-specific variant of CD44 and a protein-enabled homologue.²⁰⁶ Moreover, Rbfox2 was upregulated during the EMT, and the depletion of Rbfox2 suppressed the expression of mesenchymal marker genes.²⁰⁷

Several studies have revealed that small molecules regulate the expression of RNA-binding proteins to mediate EMT. For example, caffeine, an alkaloid in tea and coffee, reduced p53 α expression and upregulated p53 β expression through altering the expression of serine/arginine-rich splicing factor 3 to regulate EMT.⁵⁴

2.5 | Other novel mediators

Here, we present some novel mediators that contribute to EMT with the prospect of treating fibrosis and tumors. N-acetylglucosaminyltransferase, belonging to the family of glycosyltransferases, played a key role in EMT. Loss of

N-acetylglucosaminyltransferase I induced cell-cell adhesion, decreased cell migration and suppressed the expression of α -SMA, vimentin, and N-cadherin, suggesting the inhibition of EMT.²⁰⁸ Moreover, N-acetylglucosaminyltransferase I alleviated EMT induced by TGF- β 1 in human MCF-10A cells.²⁰⁹

Protein arginine methyltransferase 1 (PRMT1) mediates many essential cellular functions and plays an important role in cancer cell proliferation. Recent studies revealed that PRMT1 is a novel mediator of EMT, cancer cell migration, and invasion. Twist1 and E-cadherin are its substrates.²¹⁰ These findings strongly indicate that targeting PRMT1-mediated Twist methylation may be a new therapeutic strategy to treat fibrosis and tumors.

Histone H2A type 2-c (Hist2h2ac) was expressed in all breast cancers, and its expression was induced by EGF in the CD24⁺/CD29hi/DC44hi cell subpopulation. Hist2h2ac silencing inhibited EGF-induced ZEB1 expression and E-cadherin downregulation, which suggested that Hist2h2ac is a novel regulator of EMT in breast cancer.²¹¹

EGF-like repeat and discoidin I-like domain-containing protein 3 (EDIL3) induced EMT and promoted hepatocellular carcinoma migration, invasion, and angiogenesis *in vitro*.²¹² Furthermore, the overexpression of EDIL3 induced the activation of ERK and TGF- β signaling, and the deletion of EDIL3 suppressed EMT in lens epithelial cells through the TGF- β signaling pathway.²¹³ In addition, the cytoplasmic expression of interleukin-like EMT inducer (ILEI) is a potential marker of EMT and tumor development in colorectal cancer, and the overexpression of ILEI induced the downregulation of E-cadherin and the upregulation of vimentin.²¹⁴ Although the potential of these novel mediators in inducing tissue fibrosis and tumors has been investigated, no study has reported compounds targeting these mediators against fibrosis and tumors. Taken together, these results suggest that these novel mediators play key roles in the EMT, which will provide novel targets for small molecules in antifibrosis and antitumor research in the future.

3 | CONCLUDING COMMENTS

Both tissue fibrosis and tumors lead to high morbidity and mortality worldwide; thus, effective therapeutic strategies are urgently needed. Mounting studies have demonstrated that EMT plays a critical role in fibrosis and tumors, suggesting that drugs targeting EMT may be an effective therapy against fibrosis and tumors. Although TGF- β 1 is a potent inducer of EMT, new targets are needed due to the controversial role of TGF- β 1, which has been shown to have multiple beneficial roles in various bioactivities. As summarized above, myriad mediators, including many transcription factors (Snail, ZEB, and STAT3), signaling pathways (NF- κ B, Wnt, Akt, and PPAR), RNA-binding proteins (ESRP1 and ESRP2) and miRNAs, regulate EMT. Targeting these mediators may be a novel therapeutic strategy for antifibrosis and antitumor treatment.

Many small molecules suppress EMT by targeting these mediators, including commercial drugs and compounds derived from natural products. In addition, these compounds that target EMT have shown anticancer effects on multiple types of cancer. For example, luteolin not only attenuated gastric cancer but also showed a therapeutic effect in lung cancer cells. Therefore, we concluded that compounds targeting EMT exerted anticancer effect in one type of cancer may be effective in other types of cancer. Moreover, curcumin targeted EMT and exhibited both anticancer and antifibrotic properties, which suggests that drugs targeting EMT may exhibit both antifibrotic and anticancer effects. Taken together, these data suggest that drugs targeting EMT not only have both antifibrotic and anticancer effects but also are active against multiple types of organ fibrosis and cancer, which may assist in discovering therapeutic drugs against fibrosis and cancer.

Small molecules are a huge resource for bioactive leading compounds, and it is important to discover novel bioactive compounds effectively and quickly. Here, we summarized several methods to investigate the prospect of natural products as drug candidates. First, molecular docking is used to predict the interaction between a ligand and target protein, and molecular docking-based virtual screening is helpful to discriminate active compounds from inactive ones. In addition, during lead optimization, calculations can quickly test modifications to the structures of known active compounds before synthesis. Therefore, computational methodologies can accelerate the discovery of bioactive compounds. Second, reverse pharmacokinetics is used for drug discovery from natural products with

defined clinical benefits. Reverse pharmacokinetics can be used to guide potential target tissues/organs/molecules, and then further physiologically relevant pharmacological models are designed to discover bioactive compounds and reveal their corresponding mechanisms.

It is worth noting that many compounds show low solubility, which limits their clinical efficiency and restricts their clinical use. Fortunately, there are multiple ways to enhance the bioavailability, such as cocrystallization and the formation of phospholipid complexes and nanoemulsions.²¹⁵⁻²¹⁷

Finally, based on the hypothesis that drugs targeting EMT have both antifibrotic and anticancer effects, many important mediators contributing to EMT have been discovered. Additionally, a great number of compounds suppress EMT in tumor and fibrosis by targeting these mediators. It is hoped that many new drugs are designed and developed in the future based on the aforementioned mediators to treat tumors and fibrosis.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

AUTHOR CONTRIBUTIONS

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